Title: Patients with Diabetes and Significant Epicardial Coronary Artery Disease have Increased Systolic Left Ventricular Apical Rotation and Rotation Rate at Rest

Authors: Ravi Rasalingam MbChB[a], Mark R. Holland PhD[b] , Daniel H. Cooper MD[c], Eric Novak MS[c], Michael W Rich MD[c], James G Miller PhD[d] and Julio E Pérez MD[c]

[a] Cardiovascular Division, Boston Veterans Affairs Medical Center

[b] Department of Radiology and Imaging Sciences, Indiana University

[c] Cardiovascular Division, Washington University School of Medicine

[d] Department of Physics, Washington University in St Louis

Key Words: Myocardial strain, Echocardiography, Coronary Artery Disease, Diabetes

Total Word Count: 3,360 words

Corresponding Author: Ravi Rasalingam MD, 1400 VFW Parkway (111CA), West Roxbury, MA 02132. Telephone: Business- (857) 203-5550. E-mail- ravi.rasalingam@va.gov

Abstract

Objective: The purpose of this study was to determine whether resting myocardial deformation and rotation may be altered in diabetic patients with significant epicardial coronary artery disease (CAD) with normal left ventricular ejection fraction.

Design: A prospective observational study.

Setting: Diagnosis of epicardial CAD in diabetic patients.

Patients and Methods: 84 diabetic patients suspected of epicardial CAD scheduled for cardiac catheterization had a resting echocardiogram performed prior to their procedure. Echocardiographic measurements were compared between patients with and without significant epicardial CAD as determined by cardiac catheterization.

Main outcome measures: Measurement of longitudinal strain, strain rate, apical rotation and rotation rate, using speckle-tracking echocardiography.

Results: 84 patients were studied, 39 (46.4%) of whom had significant epicardial CAD. Global peak systolic apical rotation was significantly increased (14.9±5.1 versus 11.0±4.8 degrees, p<0.001) in patients with epicardial CAD along with faster peak systolic apical rotation rate (90.4±29 versus 68.1±22.2 degrees/sec, p<0.001). These findings were further confirmed through multivariate logistic regression analysis (global peak systolic apical rotation OR=1.17, p=0.004 and peak systolic apical rotation rate OR=1.05, p<0.001).

Conclusions: In conclusion, diabetic patients with significant epicardial CAD and normal LVEF exhibit an increase in peak systolic apical counter-clockwise

rotation and rotation rate detected by echocardiography suggesting that significant epicardial CAD and its associated myocardial effects in patients with diabetes may be detected non-invasively at rest.

Background

Patients with diabetes are at increased risk of coronary artery disease and have a higher morbidity and mortality associated with initial presentation than patients without diabetes[1,2]. Early identification and treatment of patients with CAD is therefore critical in this patient population[3].

Advances in non-invasive imaging technology have allowed more sophisticated and accurate assessment of myocardial function in patients with CAD[4]. Measurement of strain, defined as the degree of deformation of myocardium over the heart cycle relative to its initial dimension, has been shown to be abnormal by magnetic resonance imaging in patients with CAD in the absence of previous myocardial infarction[5]. The authors hypothesized that this was related to the myocardial effects of coronary atherosclerotic plaque evolution in particular involving small vessel disease, distal micro-embolization and repetitive myocardial stunning. An alternative approach to measuring myocardial strain has been developed using 2-dimensional echocardiographic images and the tracking of the relative positions of localized 'speckle' patterns seen within the myocardium as acoustic markers of deformation[6]. The degree of cardiac twisting

or rotation can also be measured by tracking the speckle pattern over the heart cycle.

Myocardial deformation is related to the fiber orientation between the different myocardial layers as well as the basal to apical levels of the heart[7,8]. Endocardial fibers are predominantly oriented in a longitudinal direction and in a right-handed helix causing left ventricular shortening predominantly[9]. Epicardial fibers are oriented in an opposing left-handed helix and exert a greater effect on myocardial twisting because of a larger radius of curvature resulting in counter-clockwise rotation at the LV apex[10]. The subendocardial layer and left ventricular apex is most vulnerable to the downstream effects of CAD remodeling, particularly in patients with diabetes prone to diffuse small vessel disease, microvascular obstruction, clinically silent myocardial ischemia and infarction[11,12]. We therefore hypothesized that rotation at the LV apex would be increased in the setting of significant CAD in patients with diabetes where the contributions from the subendocardial fibers may be compromised to a greater extent than would be the case for subepicardial fibers.

Methods

Subjects:

Consecutive patients with either type 1 or type 2 diabetes scheduled for diagnostic cardiac catheterization for suspected epicardial CAD as part of their clinical care were eligible to be enrolled in this study under a human studies

protocol approved by the Washington University Human Research Protection Office (HRPO). Diagnosis of diabetes was established by personal history and/or evidence from laboratory testing showing a random plasma glucose >200mg/dL, by fasting plasma glucose>126mg/dL, or by 2 hour oral glucose tolerance test plasma glucose >200mg/dL. Subjects were excluded from this study if they had a prior history of coronary intervention or evidence of acute or prior myocardial infarction by cardiac enzyme elevation (troponin-I ≥ 0.25 ng/ml, CK > 200 IU/L), electrocardiogram abnormality (significant Q waves, ST segment elevation or depression >1 mm in 2 contiguous leads unrelated to left ventricular hypertrophy or conduction abnormality). Patients were also excluded if resting left ventricular wall motion abnormalities were present on baseline echocardiographic examination. Other potential confounding conditions such as severe left ventricular hypertrophy defined as an end-diastolic left ventricular wall thickness >1.5 cm[13] or severe hypertension defined as systolic and diastolic blood pressures greater than 200 mmHg and 110 mmHg, respectively or ventricular conduction abnormalities at the time of acquisition were also reasons for exclusion.

Cardiac catheterization:

An experienced angiographer blinded to the echocardiographic data interpreted the results of coronary angiographic studies. The degree of stenosis was quantified by percent occlusion of the lumen as determined in two orthogonal views. For this study ≥50% of any major coronary artery indicated the presence

of significant CAD as defined by the American College of Cardiology consensus document on the performance of cardiac catheterization for evaluation of CAD[14]. This defined which patients with Diabetes were categorized as having significant CAD and which patients were in the control group with no evidence of obstructive CAD.

Echocardiography:

Transthoracic echocardiographic images were acquired using a GE Vivid 7[TM] imaging system (General Electric Medical Systems, Milwaukee, WI) immediately prior to coronary angiography. All images were obtained by an experienced sonographer and digitally archived for subsequent analyses and interpretation by a single cardiologist. Echocardiographic examination was performed which included Doppler assessment for valvular disease as well as apical four chamber (4CH), two chamber (2CH). long axis (APLAX) and parasternal short axis images of the apical region (SAX-AP). The SAX-AP was obtained by moving the transducer two intercostal spaces more caudal from the standard parasternal location. From this window an as-circular-as-possible short axis image of the LV apex was obtained just proximal to the level where end-systolic LV obliteration occurred[15]. The ejection time, based on the timing of aortic valve opening and closure, was determined by analysis of the spectral Doppler waveform obtained from a sample gate positioned in the left-ventricular outflow tract. These images were acquired for three consecutive heart cycles and downloaded to a GE EchoPac[TM] echocardiographic image analysis system (General Electric Medical Systems, Milwaukee, WI) for further analyses as

described below, including left ventricular ejection fraction.

Measurements of Myocardial Strain, Strain Rate, and Apical Rotation:

Myocardial strain (%), strain rate (s^{-1}), apical rotation (degrees) and rotation rate (degrees/sec) were obtained, by analyzing images acquired at 50-70 frames/second[16], using the GE EchoPac^{TM} analysis software by a trained investigator blinded to the patient's clinical data. Myocardial borders were delineated using the automated algorithm available on the EchoPac^{TM} system to track the myocardial thickness over the acquired heart cycles. Tracking of the myocardial borders was verified visually prior to approving the data for subsequent analysis. The systolic interval, based on the timing of aortic valve opening and closure, was determined by analysis of the spectral Doppler waveform obtained from a sample gate positioned in the left-ventricular outflow track.

Global and segmental longitudinal strain and strain rate data curves over the heart cycle were automatically measured for each apical 4CH, 2CH and APLAX echocardiographic view. The peak values for each of the global longitudinal strain (GLS) and strain rate curves (GLSr), for each of the segments in each apical view, were obtained and averaged. Also global apical rotation (GAR) and rotation rate (GARr) curves, representing the mean of the measured segments in the SAX-AP view, were generated (**Figure 1**).

Statistical Analysis:

Univariate analysis, using t-tests for independent groups, was conducted for echocardiographic variables comparing patients with significant CAD to those without. Significant CAD was defined as any stenosis ≥50% as determined by cardiac catheterization. For each echocardiographic measure a logistic regression model was built with the presence or absence of significant CAD as the dependent variable. Independent variables included the echocardiographic measurement along with covariates associated with significant CAD. To help identify covariates, the relationship between available demographic and clinical variables and significant CAD were examined through univariate analyses. Categorical variables were evaluated with chi-square tests (or Fisher's exact test in the case of small sample size cell counts). Continuous variables were evaluated with t-tests. Variables with p-values<0.10 were included as model covariates. Odds ratios and 95% confidence intervals were reported from the multivariate logistic regression analysis with one model built for each measurement. A Bonferroni correction was performed to limit the effect of multiple comparisons and type I error. Therefore, since eight variables were evaluated, echocardiographic measures were found to be significantly associated with CAD when the p-value fell below 0.05/8=0.006.

After multivariate analysis, those echocardiographic measurements that remained significant were tested for ability to identify patients with CAD, using receiver operating characteristics (ROC) analysis and the area under the curve

(AUC). The Youden index was used to identify the optimal cut-point for sensitivity and specificity[17]. Reproducibility was assessed by inter-observer and intra-observer reliability using the intra-class correlation coefficient (ICC) as well as measurement of the coefficient of variation (CV)[18]. All statistical analyses were conducted using SAS® 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Demographic Data:

A total of 123 patients were screened for eligibility. 28 patients were excluded as they did not have diabetes based on study criteria, 3 patients did not have left heart catheterization and 3 patients had reduced LV systolic function. 89 subjects were therefore enrolled of which **84** (**37** male, **47** female) ranging in age from **35** to **82** years were eligible. Poor echocardiographic windows disqualified five of the study participants. Indication for cardiac catheterization was an abnormal cardiac stress test in 89% of patients with the remainder evaluated for anginal symptoms without preceding cardiac stress testing. **Table 1** provides the clinical characteristics and conventional echocardiographic measurements of the study population. Resting heart rate tended to be lower in patients with significant CAD compared to those without significant CAD (71±13 versus 77±12 beats/minute, p=0.039) likely secondary to increased beta-blocker use (44% versus 31%, p=0.020). All other variables were similar between both groups including septal wall thickness (p=0.776) and LVEF (p=0.089). Variables with a p value <0.1 were used as covariates in subsequent multivariate logistic models.

Cardiac Catheterization Results:

39 (46%) patients had evidence of significant epicardial CAD by cardiac catheterization. The vascular distribution of significant lesions for the study population is shown in **Figure 2a**, with 19% having multi-vessel disease. The distribution of stenosis severity is shown in **Figure 2b**.

Apical Rotation and Rotation Rate:

Global apical rotation (GAR) was greater (14.9 versus 11.0 degrees) and its rate (GARr-S) was faster (90.4 versus 68.1 degrees/second) in diabetic patients with significant epicardial CAD versus those without significant epicardial CAD. After multivariate analysis controlling for systolic blood pressure, heart rate, left ventricular ejection fraction and beta-blocker use, both echocardiographic indices remained significant **(Table 2)**. GAR had an odds ratio of 1.17 (p=0.004) and GARr-S had an odds ratio of 1.05 (p<0.001). .

Longitudinal Strain and Strain Rate:

Longitudinal strain and strain rate were not significantly different between the two groups (**Table 2**).

ROC Analysis

FIGURE 3 shows ROC analyses for GAR and GARr-S. Accuracies of these parameters to detect significant CAD in the study population were assessed by measurement of the AUC; for GAR it was 0.72 (CI=0.60-0.83) and for GARr-S

was 0.74 (CI=0.63-0.85). The optimal cut-point for peak GAR was 11.7 degrees providing a sensitivity and specificity of 80.6% and 64.4% respectively. For GARr-S 71.7 seconds^{-1} provided a sensitivity and specificity of 77.8% and 64.4% respectively.

Reproducibility of Strain and Rotation Measurements:

Re-analysis of echocardiographic images from 10 patients was performed to assess inter- and intra-observer reproducibility of measurements. GAR and GLS were examined for reproducibility. Both showed good agreement with ICC values near 1. For GAR, the inter-observer and intra-observer ICC values were 0.95 (95% CI = (0.84, 0.99)) and 0.97 (95% CI = (0.9, 0.99)), respectively. For 4CH GLS, ICC = 0.97 (95% CI = (0.88, 0.99)) for inter-observer and ICC = 0.97 (95% CI = (0.89, 0.99)) for intra-observer. For inter-observer variability, the coefficient of variation (CV) for GAR is 10.0% and -3.2% for GLS. For intra-observer variability, the CV for GAR is 7.4% and -3.9% for GLS.

Discussion:

Results of our study demonstrate that resting myocardial deformation, expressed as apical rotation is increased in diabetic patients with significant CAD. These changes were detected by analysis of standard echocardiographic images.

Although LVEF remains the most commonly used measurement of LV systolic function, and is a strong predictor of prognosis in patients with CAD and heart

failure[19], this parameter depends on endocardial radial thickening and LV geometry and is insensitive to changes related to other directions of deformation[20]. Using cardiac magnetic resonance imaging, resting myocardial function has been previously shown to be abnormal in patients with sub-clinical CAD and no documented history of myocardial infarction or reduction in left ventricular ejection fraction. These studies demonstrated that patients with increased coronary artery calcification scores and carotid intimal thickness, had regional alterations in myocardial deformation and increased risk of morbidity and mortality[5,21,22]. In our study despite a trend for LVEF to be lower in patients with significant CAD (p=0.09) it was still within normal limits.

Alteration of apical rotation with significant CAD

Apical myocardial rotation and its rate were significantly increased in patients with significant epicardial CAD in our study. Patients with coronary stenosis of ≥ 50% had a mean GAR of 14.9 versus 11.0 degrees and GARr-S of 90.4 versus 68.1 degrees/second. Apical rotation in animal and human models of ischemia has been shown to transiently increase and then reduce with prolonged ischemia although the time course of these events remains unclear[23-25]. In the setting of myocardial infarction Bertini et al. demonstrated an incremental effect on subendocardial and subepicardial layers resulting in reduction of apical rotation based on the size and clinical severity of myocardial damage[26]. In patients with small infarctions compared to normal controls, subendocardial rotation was

reduced (12.6±5.2 versus 15.3±2.7 degrees) while subepicardial rotation was increased (9.6±3.6 versus 8.9±1.9 degrees). The overall effect on apical rotation specifically was not reported. There have been no studies evaluating the effects of repetitive ischemia without infarction (such as occurs with angina) on left ventricular rotation.

Interestingly, patients with diabetes without CAD have increased left ventricular apical rotation when compared to normal controls.. Fonseca et al. found a 17% increase in torsion and 20% increase in torsion rate in patients with diabetes compared to controls using cardiac MR[27]. Shivu et al. demonstrated a reduction in myocardial perfusion reserve index (MPRI) using cardiac MR in the setting of increased ventricular torsion in patients with diabetes proposing that this alteration in myocardial mechanics is related to coronary microangiopathy[29]. A reduction in MPRI has been also been demonstrated to be an accurate non-invasive measure for the presence of significant CAD[30]. Our results extend these findings suggesting that in diabetic patients with significant epicaridial CAD resting apical rotation and rotation rate detected by echocardiography are further increased.

The mechanism that underpins the observed increase in apical rotation and rate cannot be ascertained by our study. It is unlikely that these findings are related to resting myocardial ischemia with the majority of patients with significant CAD (59%) having stenoses between 50 and 90%, a severity that is unlikely to alter

resting myocardial blood flow[31]. We also did not find a significant difference in GLS and GLSr between those diabetic patients with significant epicardial CAD and those who did not (-18.5%+/-4 versus -18%+/-2.5, p=0.65). The reason for this finding is unclear. It is possible that GLS, reflecting an average of longitudinal systolic strain in the 17 segments of the heart, may not accurately reflect regional influences affecting apical rotation. Conversely the use of cardiac catheterization evaluating for obstructive disease is blind to atherosclerosis in the vessel wall. Scholte et al. in a study of 234 asymptomatic type 2 diabetic patients (57% male, 42% on insulin) demonstrated that patients with a coronary calcium score (CAC) of >0 had a significantly lower GLS (-16.3%) compared to those with a score=0 (GLS-18%)[32]. It is possible that patients with non-obstructive CAD may also have evidence of occult LV dysfunction. This in combination with diabetic cardiomyopathy and the propensity for small vessel CAD in our population where the majority of participants were female (57%) may have reduced the differences in mean GLS within our study population.

We hypothesized that patients with diabetes related cardiomyopathy develop a compensatory increase in subepicardial function when significant epicardial CAD is present secondary to repetitive myocardial ischemia, vessel remodeling and distal micro-embolization[33-35]. Others have also proposed this increase in the counter-balancing sub-epicardial function as a mechanism for increased apical rotation[36,37]. A recent study evaluating changes in myocardial mechanics in normotensive patients with type 2 Diabetes showed reduction in all vectors of

myocardial deformation except LV torsion. The authors concluded that increased torsion may provide a mechanism for preservation of LVEF despite reduction in myocardial strain[38]. As reported by a model created by Beyar et al. an increase in left ventricular rotation may provide a mechanism to reduce transmural myocardial energy requirements in the setting of reduced longitudinal deformation and sub-clinical cardiomyopathy[11].

Our findings however suggest that other mechanisms may account for an increase in apical rotation in diabetic patients with significant CAD unrelated to a reduction in sub-endocardial longitudinal deformation. Chung et. al. using tagged cardiac magnetic resonance imaging also found altered apical rotation when longitudinal shortening was unchanged in a population of type 1 diabetic patients with tight glycemic control when compared to non-diabetic patients[28]. In demonstrating normal LVEF in these patients they proposed that alteration in rotational mechanics was one of the earliest manifestations of LV dysfunction in diabetes related cardiomyopathy. They however did not assess for the presence of CAD. Our findings would suggest that the presence of CAD might also have a more significant influence on apical rotation than longitudinal deformation. A future longitudinal experiment measuring these parameters in diabetic patients as they develop CAD would help define the time-course of these changes. Park and co-workers demonstrated in patients with normal LVEF and different grades of diastolic dysfunction an increase in left ventricular torsion in patients with impaired myocardial relaxation compared to normal controls and those patients

with more severe diastolic dysfunction[39]. Their findings were principally related to an increase in apical rotation which they proposed was a compensatory mechanism along with increased untwisting to effect increased diastolic suction in patients with impaired myocardial relaxation. Increased LV filling pressures in advanced diastolic dysfunction appeared to counteract this change. In our study we did not grade the severity or influence of diastolic function on apical rotation. Our patient population however had no prior history of CAD or diastolic heart failure. Bonow and co-workers demonstrated that LV myocardial relaxation is abnormal in the presence of significant CAD despite normal LVEF and it is conceivable that this may also account for our findings of increase in apical rotation noted in diabetic patients with significant CAD without a reduction in GLS[40].

Developing an understanding of how myocardial mechanics change with the development of CAD is especially important in diabetic patients where the effects of significant epicardial CAD may further affect already impaired myocardial energetics[41]. Patients with diabetes are not only at increased likelihood of developing epicardial CAD they importantly have a poorer prognosis with first presentation of myocardial infarction with a higher incidence of heart failure and death. Our findings demonstrate that despite normal LVEF and wall motion, altered rotational mechanics exists in Diabetic patients with significant CAD. Future studies are required to further characterize the prognostic significance of altered LV rotational mechanics and the

development of CAD related sequelae.

Limitations

In this prospective study of patients with diabetes presenting for cardiac catheterization we utilized standard resting echocardiographic images acquired in a clinical setting to derive strain measurements. The relatively small study population may have affected statistical power to detect differences in the variables tested. To limit type 1 error pre-specified echocardiographic variables most likely to answer the study hypothesis were selected. This however meant other vectors of deformation such as circumferential and radial strain as well as Doppler parameters of diastolic function were not studied. A normal age and gender matched control group was also not studied to ensure that alterations in the echocardiographic variables tested were related to the presence of CAD. Comprehensive data on diabetes control was not available in our population however in the study by Chung et al. diabetes control and duration did not appear to affect the finding of increased resting torsion[28]. Finally neither quantitative angiography, intravascular ultrasound nor assessment of coronary flow reserve was performed to confirm lesion hemodynamic significance or the presence of significant negative remodeling of the artery, raising the possibility of misclassification of study participants. However, recognizing the pitfalls in accuracy of visual estimation of coronary stenosis, this study was designed to reflect current cardiology practice and data used for decision management.

Conclusions

In diabetic patients with significant epicardial CAD and normal left ventricular ejection fraction, myocardial function was characterized by an increase in LV apical counter-clockwise systolic rotation and rotation rate, suggesting that myocardial mechanics are altered with the coexistence of epicardial CAD in diabetes. These findings may have prognostic implications for the development of CAD related sequelae in Diabetic patients with ischemic heart disease. Further studies are needed to better define the mechanisms responsible for these changes, and to evaluate their potential diagnostic applicability and accuracy in a broader patient population.

Disclosures:

None.

References:

1.   Hu FB, Stampfer MJ, Solomon CG, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med.* Jul 23 2001;161(14):1717-1723.

2.   Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation.* Aug 29 2000;102(9):1014-1019.

3.   Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for coronary artery disease in patients with diabetes. *Diabetes Care.* Oct 2007;30(10):2729-2736.

4.   Saha SK, Kiotsekoglou A, Toole RS, et al. Value of two-dimensional speckle tracking and real time three-dimensional echocardiography for the identification of subclinical left ventricular dysfunction in patients referred for routine echocardiography. *Echocardiography.* May 2012;29(5):588-597.

5.   Fernandes VR, Polak JF, Edvardsen T, et al. Subclinical atherosclerosis and incipient regional myocardial dysfunction in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol.* Jun 20 2006;47(12):2420-2428.

6.   Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography--from technical considerations to clinical applications. *J Am Soc Echocardiogr.* Mar 2007;20(3):234-243.

7.   Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J.* Mar 1981;45(3):248-263.

8.   Sengupta PP, Korinek J, Belohlavek M, et al. Left ventricular structure and function: basic science for cardiac imaging. *J Am Coll Cardiol.* Nov 21 2006;48(10):1988-2001.

9.   Narula J, Vannan MA, DeMaria AN. Of that Waltz in my heart. *J Am Coll Cardiol.* Feb 27 2007;49(8):917-920.

10.   Ingels NB, Jr., Hansen DE, Daughters GT, 2nd, Stinson EB, Alderman EL, Miller DC. Relation between longitudinal, circumferential, and oblique shortening and torsional deformation in the left ventricle of the transplanted human heart. *Circ Res.* May 1989;64(5):915-927.

11.   Beyar R, Sideman S. Left ventricular mechanics related to the local distribution of oxygen demand throughout the wall. *Circ Res.* May 1986;58(5):664-677.

12.   Pfeffer MA. Left ventricular remodeling after acute myocardial infarction. *Annu Rev Med.* 1995;46:455-466.

13.   Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* Dec 2005;18(12):1440-1463.

14.   Bashore TM, Bates ER, Berger PB, et al. American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on cardiac catheterization laboratory standards. A report of the American College of Cardiology Task Force on Clinical Expert Consensus

Documents. *J Am Coll Cardiol.* Jun 15 2001;37(8):2170-2214.

15. van Dalen BM, Vletter WB, Soliman OI, ten Cate FJ, Geleijnse ML. Importance of transducer position in the assessment of apical rotation by speckle tracking echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* Aug 2008;21(8):895-898.

16. Dandel M, Lehmkuhl H, Knosalla C, Suramelashvili N, Hetzer R. Strain and strain rate imaging by echocardiography - basic concepts and clinical applicability. *Curr Cardiol Rev.* May 2009;5(2):133-148.

17. Youden WJ. Index for rating diagnostic tests. *Cancer.* Jan 1950;3(1):32-35.

18. Lachin JM. The role of measurement reliability in clinical trials. *Clin Trials.* 2004;1(6):553-566.

19. Volpi A, De Vita C, Franzosi MG, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. *Circulation.* Aug 1993;88(2):416-429.

20. Cramariuc D, Gerdts E, Davidsen ES, Segadal L, Matre K. Myocardial deformation in aortic valve stenosis: relation to left ventricular geometry. *Heart.* Jan 2010;96(2):106-112.

21. Edvardsen T, Detrano R, Rosen BD, et al. Coronary artery atherosclerosis is related to reduced regional left ventricular function in individuals without history of clinical cardiovascular disease: the Multiethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol.* Jan 2006;26(1):206-211.

22. Yan RT, Bluemke D, Gomes A, et al. Regional Left Ventricular Myocardial Dysfunction as a Predictor of Incident Cardiovascular Events MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol.* Apr 26 2011;57(17):1735-1744.

23. Jamal F, Kukulski T, Strotmann J, et al. Quantification of the spectrum of changes in regional myocardial function during acute ischemia in closed chest pigs: an ultrasonic strain rate and strain study. *J Am Soc Echocardiogr.* Sep 2001;14(9):874-884.

24. Knudtson ML, Galbraith PD, Hildebrand KL, Tyberg JV, Beyar R. Dynamics of left ventricular apex rotation during angioplasty: a sensitive index of ischemic dysfunction. *Circulation.* Aug 5 1997;96(3):801-808.

25. Kroeker CA, Tyberg JV, Beyar R. Effects of ischemia on left ventricular apex rotation. An experimental study in anesthetized dogs. *Circulation.* Dec 15 1995;92(12):3539-3548.

26. Bertini M, Delgado V, Nucifora G, et al. Left ventricular rotational mechanics in patients with coronary artery disease: differences in subendocardial and subepicardial layers. *Heart.* Nov 2010;96(21):1737-1743.

27. Fonseca CG, Dissanayake AM, Doughty RN, et al. Three-dimensional assessment of left ventricular systolic strain in patients with type 2 diabetes mellitus, diastolic dysfunction, and normal ejection fraction. *Am J Cardiol.* Dec 1 2004;94(11):1391-1395.

28. Chung J, Abraszewski P, Yu X, et al. Paradoxical increase in ventricular torsion

and systolic torsion rate in type I diabetic patients under tight glycemic control. *Journal of the American College of Cardiology.* Jan 17 2006;47(2):384-390.

29. Shivu GN, Abozguia K, Phan TT, et al. Increased left ventricular torsion in uncomplicated type 1 diabetic patients: the role of coronary microvascular function. *Diabetes Care.* Sep 2009;32(9):1710-1712.

30. Nagel E, Klein C, Paetsch I, et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation.* Jul 29 2003;108(4):432-437.

31. Gould KL, Hamilton GW, Lipscomb K, Ritchie JL, Kennedy JW. Method for assessing stress-induced regional malperfusion during coronary arteriography. Experimental validation and clinical application. *Am J Cardiol.* Oct 3 1974;34(5):557-564.

32. Scholte AJ, Nucifora G, Delgado V, et al. Subclinical left ventricular dysfunction and coronary atherosclerosis in asymptomatic patients with type 2 diabetes. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology.* Feb 2011;12(2):148-155.

33. Dokainish H, Pillai M, Murphy SA, et al. Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J Am Coll Cardiol.* Jan 4 2005;45(1):19-24.

34. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation.* Feb 8 2000;101(5):570-580.

35. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation.* Dec 18 2001;104(25):3158-3167.

36. Nakatani S. Left ventricular rotation and twist: why should we learn? *J Cardiovasc Ultrasound.* Mar 2011;19(1):1-6.

37. Sengupta PP, Tajik AJ, Chandrasekaran K, Khandheria BK. Twist mechanics of the left ventricle: principles and application. *JACC Cardiovasc Imaging.* May 2008;1(3):366-376.

38. Tadic M, Ilic S, Cuspidi C, et al. Left Ventricular Mechanics in Untreated Normotensive Patients with Type 2 Diabetes Mellitus: A Two- and Three-dimensional Speckle Tracking Study. *Echocardiography.* Jun 2015;32(6):947-955.

39. Park SJ, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK. Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* Oct 2008;21(10):1129-1137.

40. Bonow RO, Kent KM, Rosing DR, et al. Improved left ventricular diastolic filling in patients with coronary artery disease after percutaneous transluminal coronary angioplasty. *Circulation.* Dec 1982;66(6):1159-1167.

41. Shivu GN, Phan TT, Abozguia K, et al. Relationship between coronary microvascular dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. *Circulation.* Mar 16 2010;121(10):1209-1215.

Figure Legends

Figure 1. Global longitudinal strain from three apical views (Panel A, B, C). Global apical rotation was measured from a short axis view at the apex of the heart (Panel D).

Figure 2. (a) Coronary distribution of significant stenosis as determined by cardiac catheterization and **(b)** Coronary Stenosis Frequency Table.

Figure 3. ROC analysis of model based on echocardiographic parameters used for detection of significant CAD in study population.

Tables

Table 1. Clinical and echocardiographic characteristics of the study population.

		No Significant CAD		Significant CAD	
	N	Mean (± std. dev) or Count	N	Mean (± std. dev) or Count	p-value
Demographics					
Age (years)	45	58.6 (±9.3)	39	62.2(±10.6)	0.103
Male	45	19	39	18	0.717
Caucasian	45	32	39	28	1.000
Vital signs					
BMI (kg/m2)	41	36.5 (±12.3)	37	34.2 (10.1)	0.373
Height (cm)	41	168.3 (±14.9)	37	168.9 (15.4)	0.860
SBP (mmHg)	45	136 (18)	39	143 (17)	0.077
DBP (mmHg)	45	77 (11)	39	78 (12)	0.574
HR (beats/minute)	44	77 (12)	39	71 (±13)	0.039*
Risk factors					
Dyslipidemia	45	33	39	32	0.341
Smoking-current	45	11	39	9	0.960
Hypertension	45	42	39	32	0.176
Family History of CAD	44	13	39	18	0.119
Laboratory Values					
Glucose (mg/dL)	45	164.8 (±70.3)	39	185.3 (±87.3)	0.238
HgbA1c (%)	31	7.4 (±1.6)	29	8.2 (±2.7)	0.186
Creatinine (mg/dL)	44	1.13 (±1.33)	39	0.96 (±0.30)	0.436
Echocardiogram					
LVEDV (mL)	45	103.6 (±32.0)	39	100.8 (±28.7)	0.673
LVESV (mL)	45	37.4 (±13.4)	39	38.3 (±12.2)	0.754
Septum (mm)	45	1.0 (±0.1)	39	1.0 (±0.1)	0.776
LVEF (%)	45	64 (±5)	39	62 (±5)	0.089
Current Medications					
Beta-Blocker	45	14	39	22	0.020*
Calcium Channel Blocker	45	17	39	11	0.353
Angiotensin Converting Enzyme inhibitor	45	32	39	24	0.353
Oral Hypoglycemic	45	34	39	30	0.883
Insulin	45	14	39	13	0.828

Table 2. Univariate and Multivariate analysis							
		Univariate			Multivariate model		
		No CAD		Significant CAD	(for having CAD)		
Variable	N	Value±SD	N	Value±SD	Odds Ratio	P value	95% CI[†]
GAR	45	11.0±4.8	36	14.9±5.1	1.17	0.004*	1.01-1.35
GARr-S	45	68.1±22.2	36	90.4±29.0	1.05	<0.001*	1.01-1.10
GARr-E	45	-77.8±35.0	36	-89.4±39.0	0.99	0.164	0.97-1.01
GARr-A	45	-39.6±19.7	36	-50.6±33.9	0.10	0.036	0.95-1.01
GLS	45	-18.5±4.0	39	-18.0±2.5	0.97	0.647	0.78-1.19
GLSr-S	45	-1.0±0.2	39	-0.9±0.2	0.76	0.100	0.49-1.20
GLSr-E	45	1.1±0.4	39	1.0±0.2	0.96	0.616	0.77-1.20
GLSr-A	45	0.9±0.2	38	1.0±0.3	1.40	0.021	0.94-2.08

GAR=peak systolic global apical rotation, GARr-S=peak systolic global apical rotation rate, GARr-E, peak early diastolic global apical rotation rate, GARr-A=peak late diastolic global apical rotation rate, GLS=peak systolic global longitudinal strain, GLSr-S=peak systolic global longitudinal strain rate, GLSr-E= peak early diastolic global longitudinal strain rate, GLSr-A=peak late diastolic global longitudinal strain rate
* Significant at .05/8=0.006
[†] Confidence intervals calculated with Bonferroni correction

A. 4CH — Longitudinal Strain

B. 2CH — Longitudinal Strain

C. APLAX — Longitudinal Strain
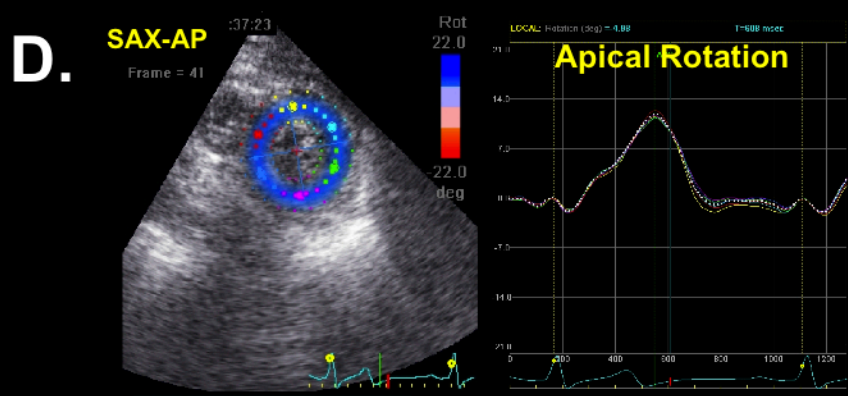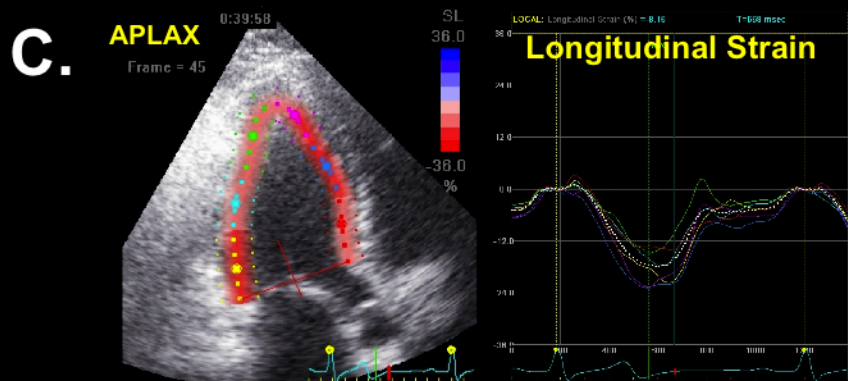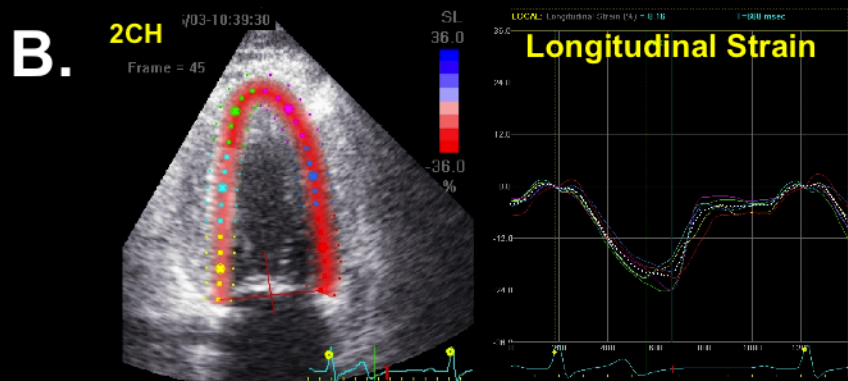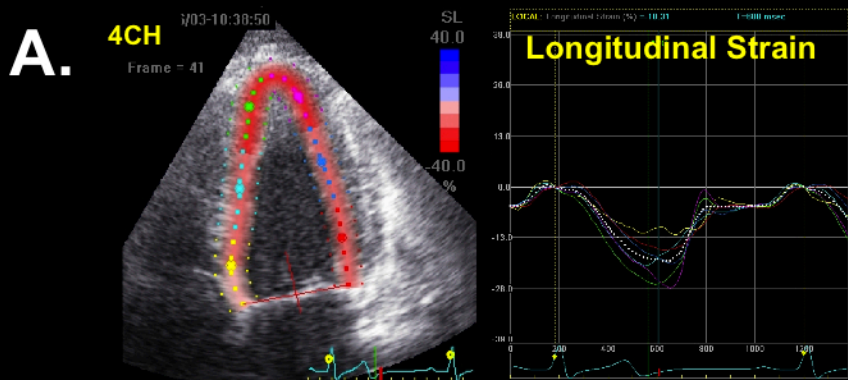
D. SAX-AP — Apical Rotation

Figure 2. (a) Coronary distribution of significant stenosis as determined by cardiac catheterization and **(b)** Coronary Stenosis Frequency Table.
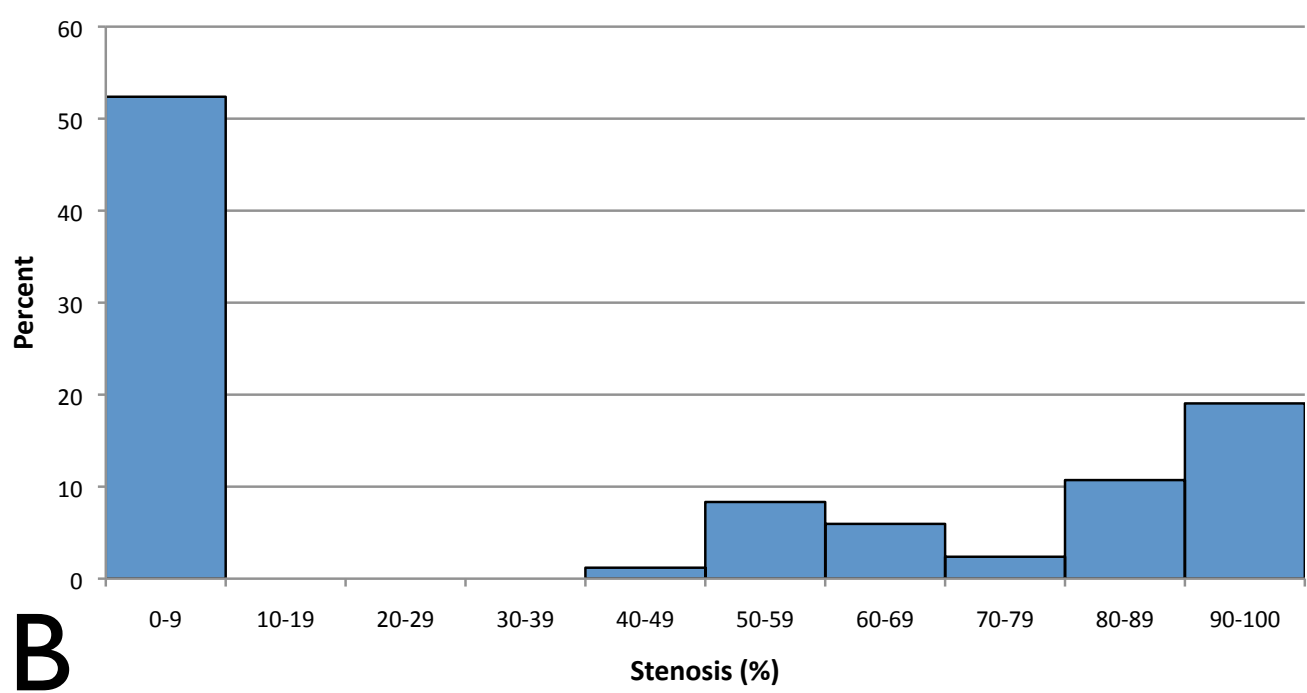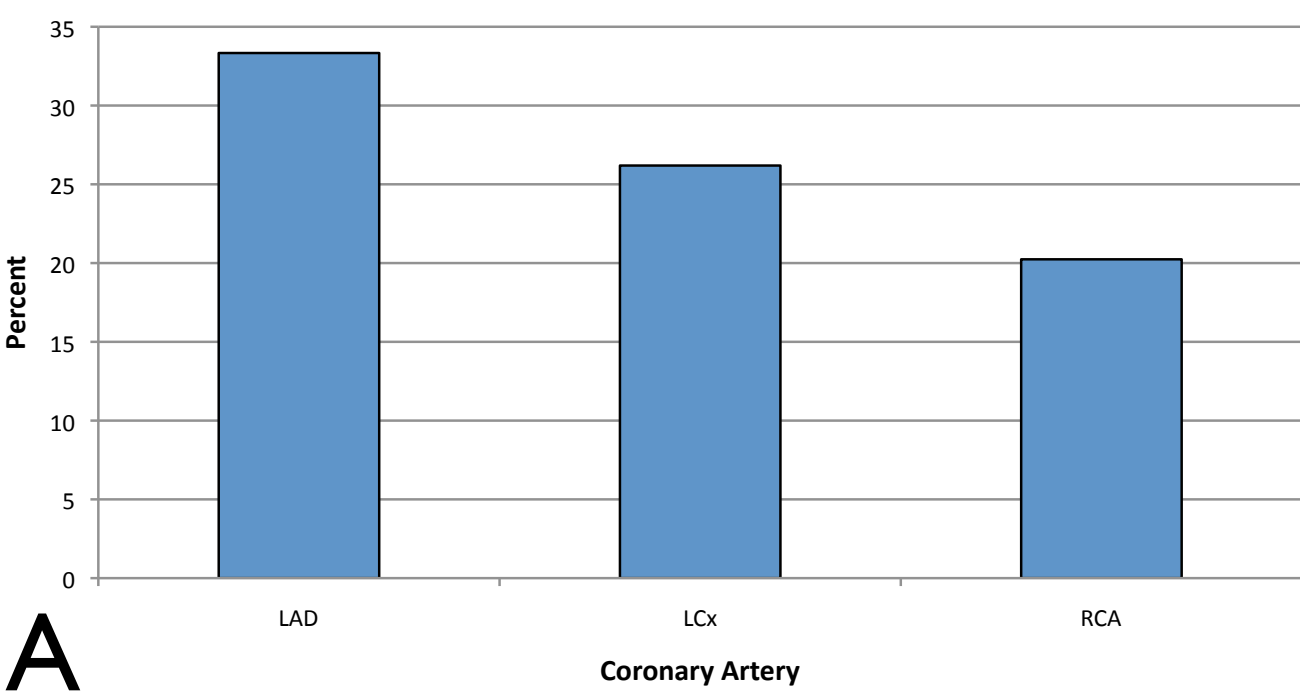
Figure 3. ROC curves for GAR and GARr-S